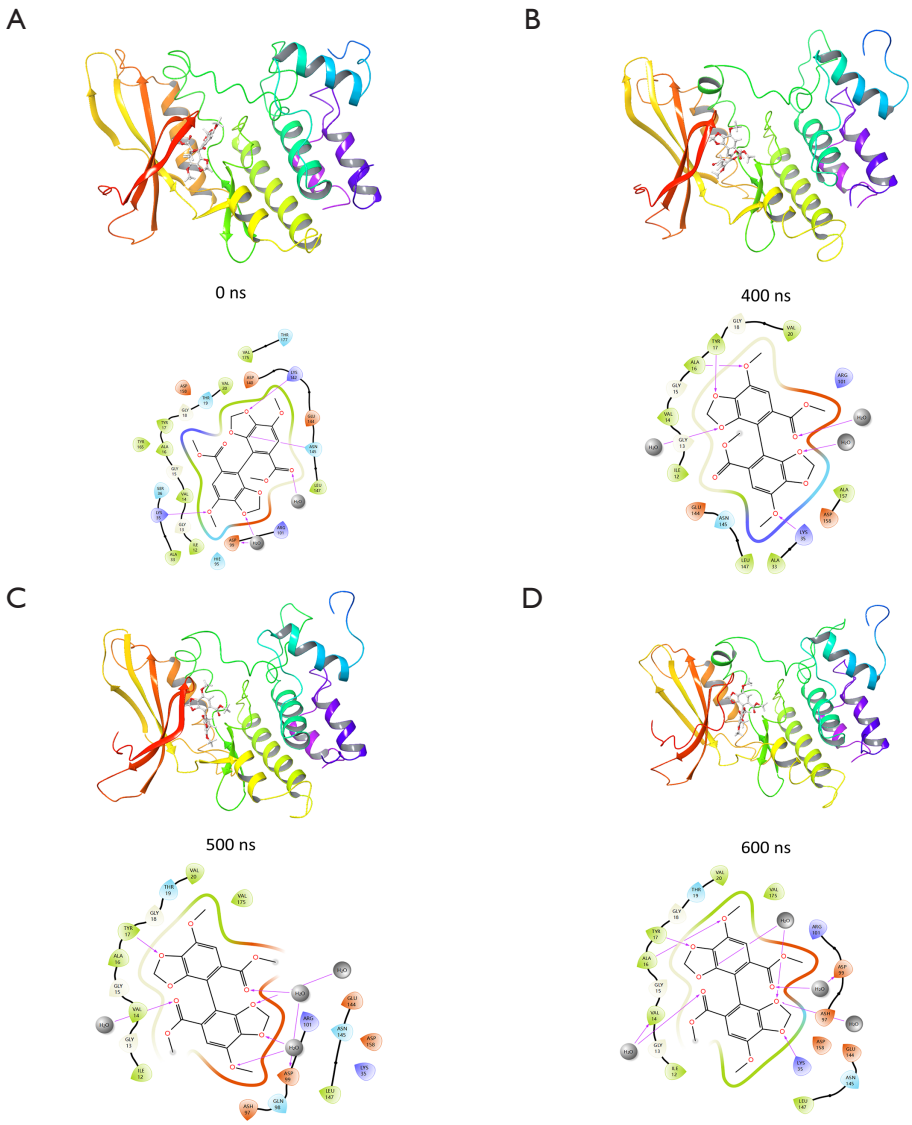

Figure S1 Snapshots of CCND1 and Bifendate complex conformations and corresponding 2D protein ligand plots sites extracted from production run trajectory at different time points.

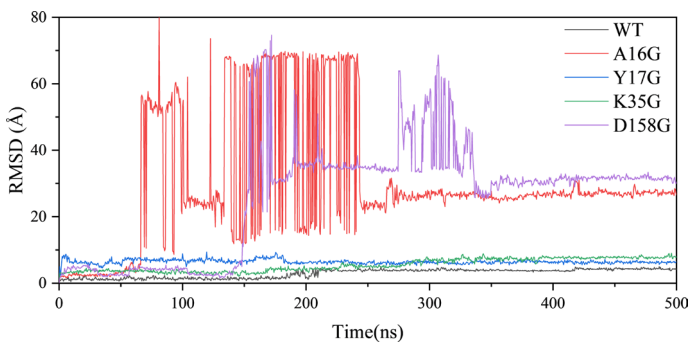

Figure S2 Protein RMSD observed in MD trajectories of Bifendate in complex with different CCND1 mutants. RMSD, root mean square deviation; MD, molecular dynamic simulation; WT, wild type

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Table S1 Details of the key interactions between compounds to their targets

Complexes	Hydrophobic interactions		Hydrogen bonds				
	Residues	Distance	Residues	Distance H-A	Distance D-A	Protein donor?	Side chain?
ADH1B-Salvigenin	Arg-47	3.94	Arg-47	2.24	3.05	Yes	Yes
	Val-203	3.68	Gly-202	2.29	3.11	Yes	No
	Val-268	3.54	Arg-369	2.79	3.21	Yes	Yes
	Val-292	3.66					
CCND1-Bifendate	Val-20	3.45	Gly-15	2.15	2.97	Yes	No
	Glu-144	3.76	Arg-101	2.66	3.14	Yes	Yes
CDK4-Xambioona	None	None	Tyr-191	1.94	2.85	Yes	Yes
EGFR-Hederagenin	Leu-694	3.65	Glu-738	2.14	2.98	No	Yes
	Val-702	3.24	Thr-766	3.32	3.78	Yes	Yes
	Val-702	3.70	Asp-776	2.50	2.98	Yes	Yes
	Ala-719	3.61					
	Lys-721	3.79					
	Thr-766	3.75					
	Thr-830	3.98					
PTGS2-Xambioona	Phe-205	3.87	Tyr-385	2.20	3.08	Yes	Yes
	Val-344	3.56	Gly-526	2.05	2.98	No	No
	Tyr-348	3.93	Gly-533	2.82	3.40	Yes	No
			Leu-534	2.51	3.29	Yes	No

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Table S2 Compound ADMET

Properties	Bifendate	Hederagenin	Xambioona	Optimal range
Molecular weight (g/mol)	418.090	472.360	388.170	100–600
Volume (Å^3)	387.061	514.542	409.607	None
Number of hydrogen bond acceptors	10	4	4	0–12
Number of hydrogen bond donors	0	3	0	0–7
Number of rotatable bonds	7	2	1	0–11
Number of rings	4	5	5	0–6
Number of atoms in the biggest ring	9	22	14	0–18
Number of heteroatoms	10	4	4	1–15
Formal charge	0	0	0	-4–4
Number of rigid bonds	22	27	28	0–30
Flexibility	0.318	0.074	0.036	None
Stereo Centers	0	9	1	≤2
TPSA (Å^2)	107.980	77.760	44.760	0–140
logS (mol/L)	–4.379	–4.126	–4.074	–4–0.5
logP (mol/L)	2.477	5.096	6.359	0–3
logD (mol/L)	2.292	4.188	5.342	1–3

ADMET, absorption, distribution, metabolism, excretion, and toxicity.

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